Oxytocin via Uniject (a prefilled single-use injection) versus oral misoprostol for prevention of postpartum haemorrhage at the community level: a cluster-randomised controlled trial

Ayisha Diop, Bocar Daff, Maimouna Sow, Jennifer Blum, Mamadou Diagne, Nancy L Sloan, Beverly Winikoff

Lancet Glob Health 2016; 4: e37–44

See **Comment** page e4

Gynuity Health Projects, New York, NY, USA (A Diop MPH, J Blum MPH, N L Sloan DrPH, B Winikoff MD); **Ministry of Health, Government of Senegal, Dakar, Senegal** (B Daff MD); **and ChildFund Senegal, Dakar, Senegal** (M Sow MA, M Diagne PhD)

Correspondence to: Ayisha Diop, Gynuity Health Projects, 15 East 26th Street, Suite 801, New York, NY 10010, USA
adiop@gynuity.org

Summary

Background Access to injectable uterotonics for management of postpartum haemorrhage remains limited in Senegal outside health facilities, and misoprostol and oxytocin delivered via Uniject have been deemed viable alternatives in community settings. We aimed to compare the efficacy of these drugs when delivered by auxiliary midwives at maternity huts.

Methods We did an unmasked cluster-randomised controlled trial at maternity huts in three districts in Senegal. Maternity huts with auxiliary midwives located 3–21 km from the closest referral centre were randomly assigned (1:1; via a computer-generated random allocation overseen by Gynuity Health Projects) to either 600 µg oral misoprostol or 10 IU oxytocin in Uniject (intramuscular), stratified by reported previous year clinic volume (deliveries) and geographical location (inland or coastal). Maternity huts that had been included in a previous study of misoprostol for prevention of postpartum haemorrhage were excluded to prevent contamination. Pregnant women in their third trimester were screened for eligibility either during community outreach or at home-based prenatal visits. Only women delivered by the auxiliary midwives in the maternity huts were eligible for the study. Women with known allergies to prostaglandins or pregnancy complications were excluded. The primary outcome was mean change in haemoglobin concentration measured during the third trimester and after delivery. This study was registered with ClinicalTrials.gov, number NCT01713153.

Findings 28 maternity hut clusters were randomly assigned—14 to the misoprostol group and 14 to the oxytocin group. Between June 6, 2012, and Sept 21, 2013, 1820 women were recruited. 647 women in the misoprostol group and 402 in the oxytocin group received study drug and had recorded pre-delivery and post-delivery haemoglobin concentrations, and overall 1412 women delivered in the study maternity huts. The mean change in haemoglobin concentrations was 3·5 g/L (SD 16·1) in the misoprostol group and 2·7 g/L (SD 17·8) in the oxytocin group. When adjusted for cluster design, the mean difference in haemoglobin decreases between groups was not significant (0·3 g/L, 95% CI −8·26 to 8·92, p=0·71). Both drugs were well tolerated. Shivering was common in the misoprostol group, and nausea in the oxytocin group. Postpartum haemorrhage was diagnosed in one woman allocated to oxytocin, who was referred and transferred to a higher-level facility for additional care, and fully recovered. No other women were transferred.

Interpretation In terms of effects on haemoglobin concentrations, neither oxytocin nor misoprostol was significantly better than the other, and both drugs were safe and efficacious when delivered by auxiliary midwives. The programmatic limitations of oxytocin, including short shelf life outside the cold chain, mean that misoprostol could be more appropriate for community-level prophylaxis of postpartum haemorrhage.

Funding Bill & Melinda Gates Foundation.

Introduction

Despite substantial progress since 1990, Senegal's maternal mortality rate of 320 per 100 000 livebirths in 2013 is still almost double its UNDP Millennium Development Goal target of 168 deaths per 100 000 livebirths.[1] Postpartum haemorrhage is the main cause of maternal mortality in Senegal: it accounts for more than 29% of maternal deaths.[2] Only around 50% of deliveries in the country (37% in rural areas) are attended by skilled personnel qualified to prevent or treat obstetric complications.[3] Additionally, lack of available trained personnel in rural areas and transport constraints make standard injectable uterotonics for the prevention and treatment of postpartum haemorrhage difficult to access.[4]

Uterotonics effectively reduce the frequency of postpartum haemorrhage.[5–6] Studies done in well resourced hospital settings show that oxytocin prophylaxis is associated with less postpartum blood loss than is misoprostol prophylaxis.[7,8] However, oxytocin is not always feasible—and might be less effective—in resource-poor settings: cool storage is necessary, and because it is given by injection, sterile equipment and skilled personnel are

Research in context

Evidence before this study

Both misoprostol and oxytocin delivered via Uniject (a prefilled, easy-to-use, single dose of oxytocin) effectively prevent postpartum haemorrhage, and, in 2011, WHO added both to its essential medicines list for this indication. We searched PubMed with the terms "postpartum haemorrhage", "misoprostol", "Uniject", and "oxytocin" for any articles published in English between Jan 1, 2010, and June 30, 2012. We also reviewed materials from organisations working on postpartum haemorrhage to be apprised of any ongoing research. We included randomised controlled studies, pre-intervention and post-intervention trials, and Cochrane reviews of either misoprostol or oxytocin; community level trials; and a review of trials in which the Uniject delivery system was used for other drugs.

Because the largest randomised controlled trials in which misoprostol was assessed were all double-blind and systematically measured blood loss, and because the assessments of oxytocin in Uniject were free of selective outcome reporting, we thought that the risk of bias was low. For all trials, data reported were complete and we found few cases of missing outcomes or loss to follow-up. We found no trials comparing oxytocin in Uniject and misoprostol at the community level.

Added value of this study

This study is the first cluster-randomised community-based trial to compare the efficacy of the two most widely used uterotonics for prevention of postpartum haemorrhage. We showed that misoprostol is not significantly less efficacious than oxytocin in Uniject when used at the community level, and reported some evidence suggesting that it might be better.

Implications of all the available evidence

In view of the programmatic limitations of oxytocin in Uniject reported in this study, the Ministry of Health in Senegal chose to introduce misoprostol for prevention of postpartum haemorrhage at maternity huts nationwide, providing uterotonic coverage where it was previously unavailable. Misoprostol is now recommended as the more pragmatic uterotonic for use at the community level. There is still no good evidence that universal prophylactic coverage with any uterotonic has a positive effect on reduction of maternal mortality.

essential.[9] Misoprostol is a safe and effective alternative,[10] and is recommended for use in settings where injectable uterotonics are neither available nor feasible.[11] Results of community-based studies have shown that misoprostol is associated with significant reductions in blood loss[12,13] and suggest that the drug could improve maternal outcomes when community-level providers are involved.[14]

Oxytocin delivered via Uniject (BIOL, Argentina) has also been investigated for prevention of postpartum haemorrhage.[15–17] This novel, simple, prefilled, single-use delivery system does not necessitate additional sterile equipment and can be used by community-level providers, thus reducing some of the limitations of standard intramuscular or intravenous administration. In community-based assessments, Uniject was safer than, and preferred to, a traditional needle and syringe, and was easily administered by all levels of providers.[15,18]

In 2011, WHO added misoprostol and oxytocin via Uniject to its essential medicines list for prevention of postpartum haemorrhage.[19] Both could help to improve access to uterotonics that are not yet widely available in rural settings in low-income countries. In a multi-site international trial in which oxytocin (given intravenously or intramuscularly) and misoprostol during the third stage of labour were directly compared, postpartum haemorrhage (defined as blood loss ≥500 mL) and severe postpartum haemorrhage (blood loss ≥1000 mL) were more common with misoprostol.[20] However, the community-based programmatic efficacy of these two uterotonic drugs has not been rigorously compared. We did this individually powered, cluster-randomised trial to determine whether oral misoprostol or oxytocin in Uniject is better at preventing postpartum haemorrhage when delivered to women in a rural, community-based setting in Senegal, where the effectiveness of oxytocin might be compromised.[21]

For the **trial protocol** see https://clinicaltrials.gov/ct2/show/NCT01713153

Methods

Study design and participants

Our study was a cluster-randomised controlled trial at 28 village-level maternity huts in three health districts in Senegal (Thiadiaye, Kolda, and Medina Yero Foula). Maternity huts are village-based health structures that are managed by an auxiliary midwife and a community health agent. In Senegal, auxiliary midwives are elected by their communities and generally receive 3–6 months of training on safe and clean delivery. All participating auxiliary midwives received an additional 3 days' theoretical training (including a clean and safe delivery refresher) and 4 days' practical training at the closest secondary level health facility. Services in maternity huts are provided in a space including a consulting area (desk and chairs) and a delivery area (delivery table). Typically, maternity huts have no instruments or medicines. Referral services are contingent on the availability of transportation in each village.

The field implementation of the study was coordinated by ChildFund Senegal. Gynuity Health Projects (new York, NY, USA) was responsible for overall study coordination. The protocol was approved by the National Council on Health Research, National Ethical Committee, Ministry of Health and Prevention, Senegal. Continuous

study monitoring and an independent data safety and monitoring board ensured protocol adherence.

Pregnant women in their third trimester were initially screened for eligibility by auxiliary midwives and ChildFund staff either during community outreach or at home-based prenatal visits. Any women delivering in a maternity hut with a study auxiliary midwife was eligible to participate.

Recruitment was integrated into community outreach sessions coordinated by nurses at the nearest health posts. Community members, such as other health workers, traditional birth attendants, and village leaders, were informed of the new drugs available and were encouraged to provide support to the study team. They were also involved in the identification of pregnant women. Women with known allergies to prostaglandins or pregnancy complications such as hypertension or haemoglobin concentrations of less than 70 g/L (in accordance with national guidelines) were advised to deliver at a higher level health facility, but those who chose not to and instead delivered at a maternity hut were included in the study. All women were given information about the trial in Wolof or Pulaar, and confirmed informed consent by signature or thumbprint. The maternity huts were randomly assigned to each study group before requesting women's consent, so participants were aware of which cluster they were in.

Except for those with an imminent need for referral, women delivering in the maternity hut who had not previously joined the study, could consent to join at time of delivery and were provided with whichever study drug the hut was randomly assigned to. This enrolment method was successfully implemented in several other community trials of postpartum haemorrhage.[12,13]

Randomisation and masking

We used cluster randomisation to reduce the risk of contamination and allow for analysis of the service offered in each randomly assigned unit. The computer-generated random allocation was overseen by Gynuity Health Projects, which also assigned clusters. Maternity huts with auxiliary midwives located 3–21 km from the closest referral centre were randomly assigned (1:1) by staff at Gynuity Health Projects to either oral misoprostol or oxytocin in Uniject, stratified by reported previous year clinic volume (deliveries) and geographical location (inland or coastal). The cluster comprised all enrolled women treated at the hut. Maternity huts that had been included in a previous study[14] of misoprostol for prevention of postpartum haemorrhage were excluded to prevent contamination. Neither auxiliary midwives nor women nor investigators could be masked to the intervention because of the differences in adminstration between the study drugs.

Study drugs were packed into individually numbered single-dose envelopes by staff at Gynuity Health Projects and supplied to maternity huts by ChildFund Senegal. Authorisation for drug importation and use was obtained from the National Pharmacy Division for the regulation of medicines.

Procedures

After informed consent was received, baseline sociodemographic and reproductive health information was gathered and haemoglobin concentrations were measured at around 8 months (±1 month); pre-delivery haemoglobin concentrations were not available for women who joined the study at delivery. Deliveries were managed according to the standard of care with the trained auxiliary midwife, who administered a single, prophylactic dose of either 600 µg oral misoprostol or 10 IU oxytocin intramuscularly via Uniject to enrolled women immediately after delivery (or after the second delivery if twins) and before delivery of the placenta.

The misoprostol (Acme, Gurgaon, India) was packaged in standard double-sided aluminium blisters and replaced as needed when it was near expiration. The oxytocin in Uniject included a time temperature indicator (TTI) to measure cumulative temperature exposure, which is related to the drug's potency. The TTI starts with a white square in a purple outer circle (stage 1), which indicates that the drug is fully potent. The square changes colour as temperature exposure accumulates to light purple (stage 2), purple (stage 3), and finally black (stage 4). The auxiliary midwives were instructed to discard devices if the inner square was the same colour as or darker than the outer circle (ie, stage 3 or 4), because such devices are not recommended for use.[18]

ChildFund regional offices refrigerated Uniject devices before field distribution (distances to maternity huts ranged from 3 km to 35 km). ChildFund study staff resupplied the maternity huts monthly or more frequently on the basis of delivery volume, and used small coolers to maintain the cold chain until arrival at the maternity hut, where all drugs were stored in dark cupboards. Because of several device stockouts early in the study and the long distances, we decided mid-study to store the Uniject devices in refrigerators at referral health posts, which were closer to the maternity huts. This strategy also allowed for greater involvement of district health posts and was more aligned with standard commodity distribution channels. All expired or damaged devices were removed and destroyed at the time of resupply.

Drug administration, including colour of TTI on the Uniject device, visual estimates of blood loss, the woman's overall condition, and any side-effects experienced were recorded on pictorial forms 2 h after delivery by the auxiliary midwives (appendix). The perceived amount of blood loss was documented as "normal", "moderate", or "significant". Referral to a higher-level facility was recommended for women experiencing continued bleeding or any symptoms suggesting the need for additional care. The auxiliary

See Online for appendix

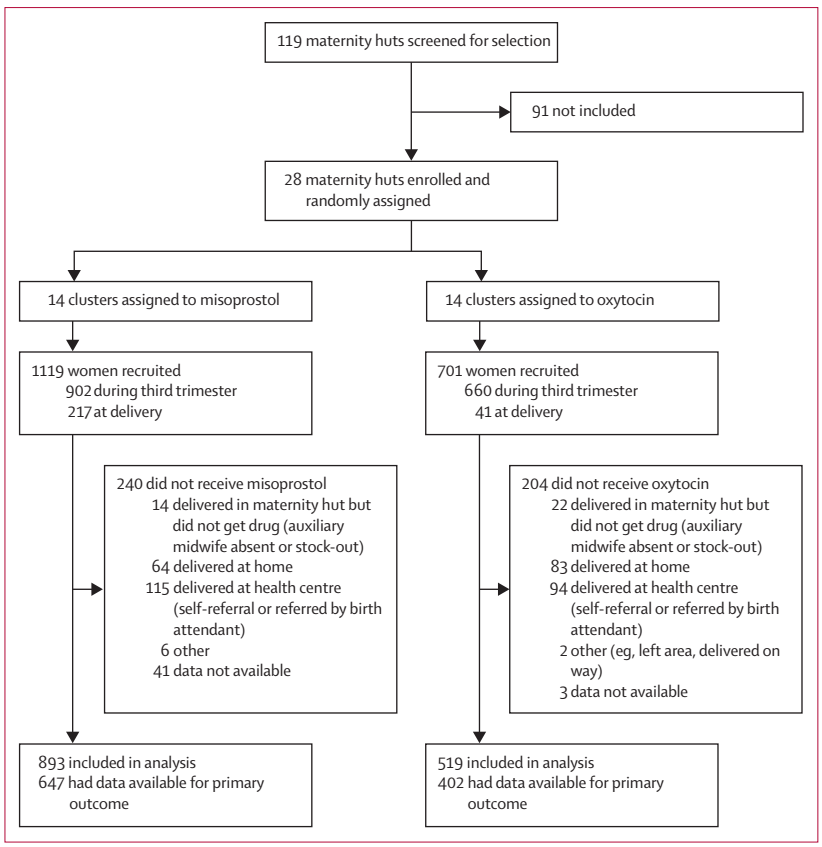

Figure 1: **Trial profile**

midwife notified study staff of each delivery. Study staff visited each woman 24–48 h after delivery to measure her haemoglobin with a Hemocue device (Angelholm, Sweden) and interview her about her condition, side-effects, and satisfaction with the drug. For women who did not deliver in the maternity hut, no follow-up data were gathered, and no data were gathered at village level to ascertain the total number of deliveries among the village population during the study.

Outcomes

The prespecified primary outcome was mean change in haemoglobin concentration in all women whose baby was delivered by an auxiliary midwife in a maternity hut in each study group. The outcome related to women on an individual (rather than a cluster) level, and was centrally assessed. Change in haemoglobin concentrations was defined as the difference between pre-delivery concentrations (measured in third trimester) and concentrations measured 24–48 h after delivery. Thus, only women in whom both pre-delivery and post-delivery haemoglobin concentrations were measured were included in the analysis. Secondary outcomes (all compared on an individual level) were falls in haemoglobin concentration of 20 g/L or more, side-effects, acceptability, and satisfaction with the treatment. Adverse events were recorded and reported as per good clinical practice.

Statistical analysis

The study was designed to test the hypothesis that either one of the regimens would produce a mean change in haemoglobin concentration 1 g/L (SD 3 g/L) greater than the other. We conservatively posited a two-tailed hypothesis. We calculated that a sample size of 282 deliveries per study group was needed to measure a significant difference between the mean haemoglobin changes with 80% power without adjusting for design (cluster) effect at an α of 0·05 (two-sided test). To adjust for design effect, the calculation of the primary outcome assumed an intracluster correlation coefficient of 0·05 and a mean cluster size of 50 (ie, 50 deliveries per cluster per year). The sample size estimated was therefore increased by a variance inflation factor of 3·45 to account for clustering (design) effects.[22] The sample was further increased by 10% to account for any protocol deviations or loss to follow-up—thus 682 deliveries (341 per group), or a total of 28 maternity huts (14 per group) were to be enrolled. Women were continuously enrolled until we attained the required number of women with complete data in both groups.

The study was planned and analysed as intention to treat, and therefore women delivering in the maternity huts were included in the primary outcome analysis irrespective of whether they received the study drugs. An intention-to-treat analysis was thought appropriate in view of the desire to assess the efficacy of two different prophylactic regimens at the community level.

All data were entered and cleaned in SPSS version 19.0. As per the study protocol, we did unadjusted analyses using Student's *t* tests or analysis of variance for continuous variables and χ^2 tests using Fisher's exact significance levels for all categorical variables. Generalised estimating equations with robust variance estimation linear and logistic regression analyses were done with and without adjustment for design effect (inland or coastal cluster randomisation and clinic volume terciles) using Stata SE version 11.0. Generalised estimating equation analysis is a robust analysis producing consistent parameter estimates irrespective of the true underlying correlation structure. The only adjustments made were for the cluster design effect (the clusters and geographical assignations were known for all women).

Role of the funding source

This study was funded by the Bill & Melinda Gates Foundation. The funder had no role in the study design; data collection, analysis, or interpretation; or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Of 119 maternity huts assessed, 28 maternity huts were randomly assigned—14 to the misoprostol group and 14 to the oxytocin group. One of the initially selected maternity huts in the oxytocin group was changed for a hut with similar characteristics (delivery volume and distance to health post) after the study was launched because the auxiliary midwife relocated to Dakar. One of the maternity huts in the misoprostol group was changed twice: the auxiliary midwife at the first hut died and the auxiliary midwife at the newly selected cluster was deemed "incompetent" by her supervisors. None of the changed sites recorded deliveries in which the study drugs were given and so contributed no participants to this analysis.

Between June 6, 2012, and Sept 21, 2013, 1820 women were recruited at these 28 maternity huts (figure 1).[23] Of the 1562 women recruited during pregnancy, 408 (26%) did not deliver in a study maternity hut. 258 women were enrolled at time of delivery. 647 women in the misoprostol group and 402 in the oxytocin group received study drug and had recorded pre-delivery and post-delivery haemoglobin concentrations (figure 1). Because of inaccuracies in service delivery statistics for the previous year and a doubling of deliveries in one high-volume maternity hut, nearly twice as many women were enrolled in the misoprostol group as the oxytocin group.

Baseline characteristics were similar in the two groups (table 1). This similarity was maintained when analysis was limited to only women with primary outcome data.

The mean change in haemoglobin concentration was 3·5 g/L (SD 16·1) in the misoprostol group and 2·7 g/L (SD 17·8) in the oxytocin group. Adjusted for cluster design, the difference in mean haemoglobin change between groups was 0·3 g/L (95% CI –8·26 to 8·92; p=0·71; table 2). The odds of experiencing a drop in haemoglobin concentrations of 20 g/L or more did not differ significantly between groups (p=0·29; table 2).

Drops in haemoglobin of 20 g/L or more seemed to be significantly associated with changes in TTI readings (table 3). 30 of the Uniject devices used were in stages not recommended for use (ie, stage 3 or 4). When analyses were limited to devices that were in the recommended TTI range, the proportion of women in whom haemoglobin concentrations fell by 20 g/L or more did not differ significantly between the misoprostol and oxytocin groups (misoprostol 5·6% *vs* oxytocin 6·6%; p=0·57).

18 stillbirths occurred during the study—six in the misoprostol group and 12 in the oxytocin group. One woman in the oxytocin group was diagnosed with postpartum haemorrhage after delivery of a stillbirth and was transferred to a health post, where she received additional doses of intramuscular oxytocin and iron supplements. She was released in a stable condition 2 days later. There were no other referrals or transfers. No other women received additional interventions after delivery, and no maternal deaths or serious adverse events were reported.

	Misoprostol (n=893)	Oxytocin (n=519)
Age	26·2 (6·2; 13–46)	25·8 (5·6; 13–42)
Previous livebirths	3·1 (2·3; 0–12)	3·1 (2·2; 0–12)
Living children	2·9 (2·1; 0–12)	2·8 (1·9; 0–10)
Prenatal visits	2·2 (1·0; 0–12)	2·1 (0·9; 0–8)
Known history of postpartum haemorrhage	183/861 (21·3%)	121/510 (23·7%)
Illiterate	507/888 (57·1%)	296/509 (58·2%)
Pre-delivery haemoglobin concentration (g/L)	98 (16; 51–168)	93 (16; 28–155)

Data are mean (SD; range) or n/N (%).

Table 1: **Baseline characteristics**

	Crude		Adjusted	
	Misoprostol (n=647)	Oxytocin (n=402)	Mean difference or odds ratio (95% CI)	p
Mean (SD) haemoglobin change (g/L)	3·49 (16·12)	2·73 (17·76)	0·33 (–8·26 to 8·92)	0·71
Decrease in haemoglobin ≥20 g/L	36 (5·6%)	35 (8·7%)	0·754 (0·450 to 1·265)	0·29

The table includes all participants who were recruited before delivery, delivered in a maternity hut, and took a study drug. We used generalised estimating equations with robust variance estimation linear and logistic regression analyses with and without adjustment for design effect.

Table 2: **Difference in haemoglobin concentration before and after delivery**

Most women experienced what auxiliary midwives visually perceived as "normal" blood loss after delivery. Bleeding classified as "moderate" or "significant" was significantly more common in the oxytocin group than in the misoprostol group (96 [19·8%] *vs* 20 [2·4%]; p<0·0001). This relation remained significant when cases in which out-of-range TTI devices (ie, stage 3–4) were excluded (18·1% *vs* 2·4%; p<0·0001). The woman diagnosed with postpartum haemorrhage received oxytocin from an expired device (stage 4); bleeding was "moderate" (n=3) or "normal" (n=26) in all other women who received oxytocin from expired devices.

Nearly all women were satisfied or very satisfied with the treatment they received at the maternity hut (table 4). Women in the misoprostol group were significantly more likely to say that they would recommend postpartum haemorrhage prevention to a friend (table 4).

Chills were significantly more common in the misoprostol group than in the oxytocin group (table 5 p<0·0001). Less than 5% of women in each group reported fever, nausea, vomiting, or diarrhoea (table 5). Six women reported severe chills in the misoprostol group and two women allocated to oxytocin reported severe fever. Nausea was significantly less common in the misoprostol group than in the oxytocin group (table 5, p<0·0001). All side-effects were well tolerated and managed at the maternity huts by auxiliary midwives. Side-effects noted by auxiliary midwives 2 h after delivery were consistent with those noted during post-delivery

	Stage 1 (n=142)	Stage 2 (n=209)	Stage 3 (n=15)	Stage 4 (n=13)
Haemoglobin decrease <20 g/L	135 (95%)	193 (92%)	13 (87%)	8 (62%)
Haemoglobin decrease ≥20 g/L	7 (5%)	16 (8%)	2 (13%)	5 (39%)

Data are n (%). Some percentages do not add to 100% because of rounding. p<0·0001 for a dichotomously tested "use" for stage 1 and 2 versus "do not use" for stages 3 and 4.

***Table 3*: Decrease in haemoglobin concentrations after administration of oxytocin, by Uniject time temperature indicator stage**

	Misoprostol (n=880)	Oxytocin (n=490)	p
Study drug given at correct time	878/879 (99·9%)	487/487 (100%)	0·98*
Problems related to administration	0/781	2/470 (0·4%)	0·14*
Satisfied or very satisfied with drug	854/854 (100%)	480/484 (99·2%)	0·002
Complaints about or problems with drug	18/858 (2·1%)	28/481 (5·8%)	0·0002
Would take drug again after subsequent deliveries	833/834 (99·9%)	457/461 (99·1%)	0·06*
Would recommend drug to a friend	812/812 (100%)	451/454 (99·3%)	0·05*

Data are n/N (%). The different denominators used show actual data recorded. The data in the first two rows were provided by auxiliary midwives, whereas the rest was reported by women. All women who received study drug were included. *Excludes women who were not provided with the study drug; these data were dichotomously tested.

***Table 4*: Use and acceptability of study drugs**

	Crude		Adjusted odds ratio (95% CI)	p
	Misoprostol	Oxytocin		
Chills	531/658 (61·4%)	25/484 (5·2%)	37·634 (8·653–163.679	<0·0001
Fever	26/869 (3·0%)	7/485 (1·4%)	1·892 (0·159–22·565)	0·61
Nausea	10/869 (1·2%)	6/487 (1·2%)	0·770 (0·751–0·790)	<0·0001
Vomiting	6/869 (0·7%)	1/487 (0·2%)	2·877 (0·085–97·331)	0·56
Diarrhoea	3/869 (0·3%)	3/487 (0·6%)	0·737 (0·159–3·420)	0·70
Bleeding 2 h after birth			0·151 (0·044–0·514)	0·002
Normal	831/851 (97·6%)	389/485 (80·2%)		
Moderate	20/851 (2·4%)	87/485 (17·9%)		
Significant	0/851	9/485 (1·9%)		

Data are n/N (%). Bleeding was observed and classified by auxiliary midwives. The different denominators used show actual data recorded. We used generalised estimating equations with robust variance estimation linear and logistic regression analyses with and without adjustment for design effect.

***Table 5*: Reported side-effects**

follow-up by study staff (data not shown). One woman was given misoprostol before rather than after delivery, but neither she nor the baby had any adverse effects (table 4).

More women in the oxytocin group than in the misoprostol group complained or had concerns about their treatment (28 of 481 [5·8%] *vs* 18 of 858 [2·1%]; p=0·0002). More than 99% of women in both study groups would take their assigned drug again (table 4). 14 of the 28 complaints raised by women receiving oxytocin in Uniject focused on injection site pain; eight of 18 complaints about misoprostol were about shivering. All women who complained about shivering after misoprostol were "satisfied" or "very satisfied" with the treatment. Three of those who complained about injection site pain in the oxytocin group were among those "not satisfied" with their treatment.

Auxiliary midwives generally reported no difficulties with storing or administering misoprostol correctly and were confident in their capacity to use it. Oxytocin in Uniject posed some challenges. Additional logistic measures were implemented to resupply devices and maintain the cold chain for oxytocin, which increased distribution costs and wastage and would complicate public health programmes. Despite these efforts, expired or late-stage Uniject devices remained at the maternity huts and were inevitably used when more appropriate Uniject devices were unavailable. Monitoring reports suggest that roughly 32% of the Uniject devices supplied had to be replaced in the maternity huts because they were no longer recommended for use (data not shown). Some providers had difficulty opening the packaging of the Uniject device, and one auxiliary midwife was not allowed to participate in the study because she was unable to hold the device and administer the drug correctly (she was retrained and provided with more supervision).

Discussion

In our trial, neither 600 µg oral misoprostol nor 10 IU oxytocin delivered via Uniject by auxiliary midwives was significantly better in terms of their effect on mean change in haemoglobin concentrations in postpartum women—the primary outcome. Our results show that either drug can be correctly and safely offered by auxiliary midwives for prevention of postpartum haemorrhage, as previously shown by data for misoprostol in Senegal and for oxytocin in Uniject in Ghana.[14,24] Both methods are feasible and easy to use, but our results suggest that misoprostol might have some advantages over oxytocin via Uniject at the community level.

Consistent with previous studies of oxytocin in Uniject,[24,25] additional efforts were necessary to try to maintain the cold chain at the community level. In rural Ghana, a study[25] of the effect of heat exposure on Uniject showed that devices could expire in as few as 6 days or last as long as 59 days, depending on temperature and storage conditions. In two simulations in that study, 16% and 34% of devices needed to be discarded after 30 days; 6% of devices used were already expired when they were delivered.[25] In large-scale service delivery programmes, resupply, preservation of cold chain, and communication can vary, leading to increased wastage and use of ineffective devices.

A substantial proportion of women receiving misoprostol experienced transient shivering, which was deemed acceptable in our trial. Shivering was managed in the maternity huts by using extra cloths or head

scarves brought by the woman, and no additional drugs were needed. Community programmes in which misoprostol is given should provide information and counselling about management of fever and shivering.

Community involvement was an important aspect of this study. In addition to helping to identify pregnant women, community members, such as the health workers, traditional birth attendants, and village leaders, had roles in delivery plans and funds for drugs, care, and transport.

During our study, misoprostol was registered for prevention and treatment of postpartum haemorrhage and became commercially available in Senegal, international recommendations—including those of the International Federation of Gynecology and Obstetrics[26]—were released, and misoprostol was added to Senegal's Essential Medicines List.[27] Oxytocin in Uniject continues to be unavailable in most jurisdictions. For now, commodity security for consistent prevention of postpartum haemorrhage is more likely in circumstances where misoprostol is the first-line drug for use at the community level.

In 2013, the Senegalese Ministry of Health created the Division of Community Health, which developed a national strategic plan for 2014–18 in response to challenges faced in providing services at the community level. Several of the plan's strategies sought to address the role of community-level providers, such as auxiliary midwives and birth attendants. When we began this study, auxiliary midwives were not formally recognised in the Senegalese health-care system and were not thought to be qualified to dispense medication. At study completion, a committee appointed by the Ministry of Health reviewed our findings and recommended that misoprostol be made available to auxiliary midwives for provision after delivery in maternity huts nationwide. Supervision will be needed to ensure that quality of care is maintained as the programme expands.

A limitation of our study is that only women who delivered in study maternity huts with an auxiliary midwife were enrolled. In view of the practical limitations of research in rural community settings, we could not gather post-delivery data for women who did not deliver at the maternity hut with a study auxiliary midwife and therefore we cannot report on the broader effects of the intervention on the entire population of women in each cluster area. Furthermore, we could not gather reliable population-level data throughout the course of the study, so we cannot report on community-level uterotonic coverage.

The selection of a cluster-randomised trial without masking is another potential weakness. Overall, we thought that a cluster-randomised trial would limit exposure to potential biases and trial errors that might be inevitable in a community-based, double-blind randomised controlled trial in view of the two very different methods of drug delivery: a pill and an injection. For instance, we purposefully avoided selection of maternity huts with previous experience of use of misoprostol for prevention of postpartum haemorrhage. As there was nearly universal appropriate application of both misoprostol and oxytocin in Uniject and no biological basis to assume that women's satisfaction would affect their haemoglobin concentrations, we conclude that the lack of masking had little, if any effect, on the primary outcome. The secondary outcomes (particularly side-effects) are also consistent with findings from other studies comparing misoprostol and oxytocin,[20] and also suggest little or no bias due to study design.

Although oxytocin is more efficacious than misoprostol for prophylaxis in hospital-based studies,[28] in the face of conditions in rural communities in low-resource settings, the advantages of oxytocin could be diminished or possibly reversed. Ease of use, higher acceptability, and fewer logistic constraints make misoprostol a more adaptable option at the community level. Furthermore, because of the poor availability of oxytocin in Uniject, standard intramuscular delivery of oxytocin would have to be used instead, which would present even greater challenges in terms of training, logistics, and storage in rural settings.[29]

Maximisation of the potential of human resources at all levels of the health-care system is essential to reduce the burden of maternal morbidity and mortality. Provision of misoprostol prophylaxis for postpartum haemorrhage at the community level is a proven strategy that can contribute to global efforts.[30]

Contributors

JB, BW, and AD contributed to design of the original research. MS, MD, and AD were responsible for study implementation and data collection. NLS and AD did the data analysis. JB and AD drafted the manuscript. All authors contributed to the interpretation of results.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank the women who participated in this trial; the auxiliary midwives who provided care; ChildFund field staff who carefully gathered the data, the field supervisors, and Ndèye Mbow in particular; the regional medical directors of Thiès and Kolda; the regional and district reproductive health coordinators of Thiès, Thiadiaye, and Medina Yero Foula for helping with all field activities, training, and supervision; the individuals who provided support and guidance from the Health Program USAID Dakar, USAID Kolda Regional Office, and the Maternal Health Division of the Ministry of Health; Jill Durocher, Meagan Byrne, and Tara Shochet of Gynuity Health Projects; Allan Donner of the Western University, London, Canada; and staff at Marie Stopes International, Senegal for assisting with Misoclear provision.

References

1 WHO, UNICEF, UN Population Fund, World Bank, UN Population Division Maternal Mortality Estimation Inter-Agency Group. Maternal mortality in 1990–2013: Senegal. http://www.who.int/gho/maternal_health/countries/sen.pdf?ua=1 (accessed Oct 10, 2014).

2 Ndiaye S, Ayad M. Enquête démographique et de santé au Sénégal 2005. Calverton, MD: Centre de Recherche pour le Développement Humain and ORC Macro, 2006.

3 Agence Nationale de la Statistique et de la Démographie, ICF International. Enquête démographique et de santé continue 2012–2013. Calverton, MD: Agence Nationale de la Statistique et de la Démographie and ICF International, 2012.

4 Cheikh M, Derriennic Y, Diouf F, Demba DA, Diawara L, Diagne A. Evaluation du système de santé du Sénégal. Bethesda, MD: Abt Associates, 2009.

5 Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. *Cochrane Database Syst Rev* 2012; **8:** CD000494.

6 Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. *Cochrane Database Syst Rev* 2014; **2:** CD003249.

7 Alfirevic Z, Blum J, Walraven G, Weeks A, Winikoff B. Prevention of postpartum hemorrhage with misoprostol. *Int J Gynaecol Obstet* 2007; **99** (suppl 2)**:** S198–201.

8 Gülmezoglu AM, Forna F, Villar J, Hofmeyr GJ. Prostaglandins for preventing postpartum haemorrhage. *Cochrane Database Syst Rev* 2007; **3:** CD000494.

9 Tsu VD, Langer A, Aldrich T. Postpartum hemorrhage in developing countries: is the public health community using the right tools? *Int J Gynaecol Obstet* 2004; **85** (suppl 1)**:** S42–51.

10 Walraven G, Blum J, Dampha Y, et al. Misoprostol in the management of the third stage of labour in the home delivery setting in rural Gambia: a randomised controlled trial. *BJOG* 2005; **112:** 1277–83.

11 WHO. Recommendations for the prevention and treatment of postpartum haemorrhage. Geneva: World Health Organization, 2012. http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548502/en/ (accessed Feb 12, 2015).

12 Mobeen N, Durocher J, Zuberi NF, et al. Administration of misoprostol by trained traditional birth attendants to prevent postpartum haemorrhage in homebirths in Pakistan: a randomised placebo-controlled trial. *BJOG* 2011; **118:** 353–61.

13 Derman RJ, Kodkany BS, Goudar SS, et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. *Lancet* 2006; **368:** 1248–53.

14 Diadhiou M, Dieng T, Ortiz C, Mall I, Dione D, Sloan NL. Introduction of misoprostol for prevention of postpartum hemorrhage at the community level in Senegal. *Int J Gynaecol Obstet* 2011; **115:** 251–55.

15 Tsu VD, Sutanto A, Vaidya K, Coffey P, Widjaya A. Oxytocin in prefilled Uniject injection devices for managing third-stage labor in Indonesia. *Int J Gynaecol Obstet* 2003; **83:** 103–11.

16 Althabe F, Mazzoni A, Cafferata ML, et al; Oxytocin in Uniject Study Group. Using Uniject to increase the use of prophylactic oxytocin for management of the third stage of labor in Latin America. *Int J Gynaecol Obstet* 2011; **114:** 184–89.

17 Tsu VD, Luu HT, Mai TT. Does a novel prefilled injection device make postpartum oxytocin easier to administer? Results from midwives in Vietnam. *Midwifery* 2009; **25:** 461–65.

18 Prevention of Postpartum Hemorrhage Initiative. Pilot use of oxytocin in a Uniject device for AMSTL in Mali: evaluation of the safety and feasibility of a new delivery technology. Seattle: PATH, 2008.

19 WHO. Unedited report of the 18th expert committee on the selection of use of essential medicines, 21 to 25 March 2011, Accra, Ghana. http://www.who.int/medicines/publications/unedited_trs/en/index.html (accessed Oct 20, 2014).

20 Gülmezoglu AM, Villar J, Nhu Ngoc NT, et al. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. *Lancet* 2001; **358:** 689–95.

21 Buekens P, Althabe F. Post-partum haemorrhage: beyond the confrontation between misoprostol and oxytocin. *Lancet* 2010; **375:** 176–78.

22 Donner A, Klar N. Design and analysis of cluster randomized trials in health research. London: Arnold, 2000.

23 Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. *BMJ* 2004; **328:** 702–08.

24 Stanton CK, Newton S, Mullany LC, et al. Impact on postpartum hemorrhage of prophylactic administration of oxytocin 10 IU via Uniject by peripheral health care providers at home births: design of a community-based cluster-randomized trial. *BMC Pregnancy Childbirth* 2012; **12:** 42.

25 Mullany LC, Newton S, Afari-Asiedu S, et al. Cumulative effects of heat exposure and storage conditions of oxytocin-in-Uniject in rural Ghana: implications for scale up. *Glob Health Sci Pract* 2014; **2:** 285–94.

26 International Federation of Gynecology and Obstetrics. Prevention of postpartum hemorrhage with misoprostol. *Int J Gynaecol Obstet* 2012; **119:** 213–14.

27 Ministère de la santé et de l'action sociale, Direction de la pharmacie et du médicament. Liste nationale de médicaments et produits essentiels du Sénégal. Révision de 2013. http://apps.who.int/medicinedocs/documents/s20181fr/s20181fr.pdf (accessed Nov 2, 2014).

28 Atukunda EC, Siedner MJ, Obua C, Mugyeny GR, Twagirumukiza M, Agaba AG. Sublingual misoprostol versus intramuscular oxytocin for prevention of postpartum hemorrhage in Uganda: a double-blind randomized non-inferiority trial. *PLoS Med* 2014; **11:** e1001752.

29 Stanton C, Nand DN, Koski A, et al. Accessibility and potency of uterotonic drugs purchased by simulated clients in four districts in India. *BMC Pregnancy Childbirth* 2014; **14:** 386.

30 Oladapo O. Misoprostol for preventing and treating postpartum hemorrhage in the community: a closer look at the evidence. *Int J Gynaecol Obstet* 2012; **119:** 105–10.